Greater short-term weight loss in women 20-45 versus 55-65 years of age following bariatric surgery

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Abstract: BACKGROUND: Whether and how sex and age affect bariatric-surgery outcome is poorly understood. Estrogens regulate body composition in women and animals, and increase weight loss in a rodent model of gastric bypass, suggesting that premenopausal women may lose more weight following bariatric surgery. METHODS: One thousand three hundred fifty-six female gastric-bypass or gastric-banding patients were retrospectively grouped as 20-45 years old (presumptively premenopausal; n = 1,199) and 55-65 years old (presumptively postmenopausal; n = 157). Mixed-model ANCOVA followed by Bonferroni-corrected t tests were used to categorically test the effect of age on percent excess body weight loss (%EBWL) at 1 and 2 years post-surgery, controlling for preoperative EBW and surgery type. Age effects were also tested dimensionally in all women and in 289 male patients. RESULTS: Twenty- to forty-five-year-old women showed greater %EBWL 1 and 2 years post-surgery than 55-65-year-old women (p's < 0.0005). No age effect was detected in 20-25- vs. 30-35-, 30-35- vs. 40-45-, or 20-25- vs. 40-45-year-old women (p's > 0.2) This age effect was detected only after gastric banding, with 20-45-year-old women losing 7 kg more than 55-65-year-old women after 2 years. Dimensional analysis confirmed a significant inverse effect of age on bariatric surgery outcome in women, but did not detect any effect in men. CONCLUSIONS: Results indicate that 55-65-year-old women lose less weight than 20-45-year-old women in the initial 2 years after bariatric surgery, especially gastric banding; this may be mediated by age- or menopause-associated changes in physical activity, energy expenditure, or energy intake.

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Reduced Effectiveness of Bariatric Surgery in Postmenopausal-Age Women

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Short Title: Menopausal Age and Bariatric Weight Loss

Abstract

Background Estrogens regulate lean and adipose tissue masses in women and animals, and led to increased weight loss in a rodent model of gastric bypass, suggesting that pre- vs. post- menopausal-age women may lose more weight following bariatric surgery.

Methods 1,356 obese women who underwent gastric bypass or banding were retrospectively categorized into premenopausal-age (20-45 y; n = 1199) and postmenopausal-age (55-65 y; n = 157) groups. Mixed-model ANCOVA was used to test the effect of menopausal age (pre vs. post) on the percent of excess body weight loss (%EBWL) at 1 and 2 y post-surgery. Bonferroni-corrected t-tests were conducted for between-subjects pairwise comparisons at different time points. Analyses controlled for preoperative excess body weight and surgical type.

Results Holding procedure type and preoperative percent excess body weight constant, pre- vs. post- menopausal-age women showed greater %EBWL lost at both 1 and 2 y post-surgery (both p's < 0.0005). This effect was not seen between women 20-25 vs. 30-35 y, 30-35 vs. 40-45 y, or 20-25 vs. 40-45 y of age (all p's > 0.2). Interestingly, the effect of premenopausal-age was detected only in gastric banding patients and not in gastric bypass patients, with pre- vs. post- menopausal-age gastric banding patients losing about 7 kg more at 24 mo post-surgery.

Conclusions Results are consistent with the hypothesis that menopausal status may affect weight loss after gastric banding surgery.

Keywords estrogen, menopause, gastric bypass, gastric banding, RYGB

Introduction

Bariatric surgery is currently the only effective means to reverse morbid obesity, and its use continues to increase in the US and other countries [1, 2]. Although it is not widely discussed, there is a marked disparity in the number of men and women who elect bariatric surgery. In the USA, for example, more than 80% of bariatric surgery patients are women [3, 4]. This difference, together with many data in humans and animals indicating that female reproductive-axis function potently influences eating and body weight regulation [5, 6], suggests the importance of determining whether female reproductive axis function influences bariatric surgery outcome. To our knowledge, however, no such study has been reported.

A prominent example of the influence of reproductive physiology on body weight regulation is the increase in adiposity that accompanies menopause. Studies that statistically segregate the effects of aging *per se* and menopausal status indicate that menopause is associated with a ~5-10% increase in adiposity [7-10]. Furthermore, this increase seems to occur predominately in intra-abdominal adiposity, which has more deleterious metabolic effects than subcutaneous adiposity [11]. The effect of menopause on bariatric surgery outcome has not been studied, but estradiol treatment increased weight loss in a rat model of gastric bypass [12]. Therefore, we performed a preliminary analysis of the changes in excess body weight following gastric bypass and banding procedures in a series of pre- and post- menopausal-age women treated at a university medical center.

Materials and Methods

Participants

The overall sample consisted of 1,787 women and 289 men, 18-65 y of age, who underwent either laparoscopic Roux-en-Y gastric bypass (RYGB) or laparoscopic gastric banding between May 1, 2001 to May 1, 2011 at the Center for Bariatric Surgery and Metabolic Diseases at St Luke's Hospital, NY, NY, a level 1A center for excellence in bariatric surgery. All patients met the criteria for bariatric surgery proposed by the National Institutes of Health Consensus Panel in 1991 [13]. Because of the lack of specific data identifying the onset of menopause, women were classified as presumptively premenopausal (< 45 y of age) or presumptively postmenopausal (> 55 y), yielding 1,199 women between 18-45 y old in the premenopausal-age group and 157 women between 55-65 y old in the postmenopausal-age group. Men and patients between 45 and 55 y of age were not included in categorical analyses. Baseline characteristics of the 1,356 participants are described in Table 1.

Design

Excess body weights were computed at 1 wk pre-surgery, and 12 and 24 mo post-surgery, and a retrospective analysis of percent excess body weight loss (%EBWL) was conducted using sex, age and surgery type to classify the patients. Excess body weight was defined as measured body weight minus the body weight that would result in a

body mass index (BMI) of 25 kg/m^2, the upper limit of the normal range [14]. This study was approved by the St Luke's Roosevelt Hospital Institutional Review Board.

Statistical Analyses

Data were analyzed using mixed-model analyses of covariance (ANCOVA) followed by Bonferroni-corrected pairwise comparisons, with time (baseline, 12 and 24 mo post-surgery) included as a within-groups factor and menopausal age (pre vs. post) as a between-groups factor. ANCOVAs were conducted controlling for preoperative excess body weight and surgery type (RYGB, gastric banding). Surgery type was included as a between-subjects factor in order to test whether the effect of menopausal age on postoperative weight loss varied by procedure type.

In order to test the specificity of the effect of age for pre- vs. post- menopausal-age women, ANCOVAs were repeated with different age groupings (20-25 vs. 30-35 y old women, 30-35 vs. 40-45 y old women, and 20-25 vs. 40-45 y old women) as the between-groups factors. Although there was insufficient power to assess an effect of age in men categorically (n = 218 in the < 45 y old group and n = 18 in the > 55 y of age group, yielding only 11% power), there was adequate power to test an effect of age dimensionally in both men (n = 289) and women (n = 1787). Age was regressed on %EBWL, with preoperative excess body weight and procedure type included in the model as covariates. All tests were two-tailed, with $\alpha = 0.05$ and multiple imputation [15, 16] used for missing values.

Results

Effect of Pre- vs. Post- Menopausal-Age

Holding procedure type and preoperative percent excess body weight constant, pre- vs. post- menopausal-age women showed greater %EBWL women at both 12 and 24 mo after bariatric surgery (overall $F_{1,1355} = 6.9$, $p = 0.001$; 12 and 24 mo p's < 0.0005).

Specificity of Effect of Pre- vs. Post- Menopausal-Age

To determine whether the effect of age stratification on bariatric surgery outcome was specific to menopausal age, similar analyses were done contrasting 20-25 vs. 30-35 y old women, 30-35 vs. 40-45 y old women, and 20-25 vs. 40-45 y old women. None of these contrasts were significant (all ps > 0.2). Testing dimensionally, while controlling for procedure, age inversely predicted %EBWL in women at 12 mo ($t_{1783} = -3.6$; $p < 0.0001$) and 24 mo ($t_{285} = -2.5$; $p = 0.012$) post-surgery. However, age did not predict %EBWL in men at 12 or 24 mo post-surgery (both ps > 0.3).

Effect of Surgical Procedure

A three-way interaction was observed between menopausal age, time and surgery type, prompting individual (corrected) comparisons of RYGB and gastric banding patients. Percent excess body weight loss was greater in pre- vs. post- menopausal-age women

undergoing gastric banding both 12 and 24 mo post-surgery (overall $F_{1,323} = 4.2$, $p = 0.016$; Figure 1), which translated into about a 7 kg increase in weight loss in pre- vs. post- menopausal-age women at 24 mo post-surgery. However, this effect was not detected in women undergoing RYGB (overall $p = 0.24$; Figure 1).

Results did not depend on the choice of relevant dependent or control variables. The same pattern of effects was detected when analyses were conducted with preoperative %EBW, weight or BMI included as covariates. Similarly, results did not differ when using total body weight loss (TBWL) or %TBWL as the outcome variable.

Discussion

We report novel evidence suggesting that menopausal status may affect bariatric surgery outcome. Percent excess body weight loss was significantly greater in pre- vs. post- menopausal-age women at 1 and 2 y follow-up. In contrast, analyses of women 25-45 y of age failed to reveal any effect of age on bariatric surgery outcome. Similarly, dimensional analyses of men revealed no effect of age. The failure to find effects in these adequately powered specificity analyses suggests that the difference between 25-45 y-old women and 55-65 y-old women was related to menopausal status rather than chronological age. However, alternative factors, such as the age-related decrease in metabolic rate, cannot be ruled out. Basal metabolic rate decreases more rapidly in women than men, especially around age 50, and the extent to which this is menopause-related is unknown [6, 17, 18].

Surprisingly, the effect of menopausal age on outcome depended on surgery type; significant effects were detected in women undergoing gastric banding, but not RYGB. The failure to detect a significant menopausal-age effect in RYGB patients may have been due to the difference in postoperative weight loss between RYGB and gastric banding (i.e., %EBWL was greater after RYGB than after gastric banding both 12 and 24 mo post-surgery).

The current data suggest that menopausal status may account for some of the variance in postoperative weight loss following at least one form of bariatric surgery in women. Our observation that estradiol treatment increased weight loss in ovariectomized rat undergoing gastric bypass [12] suggests the menopause-related reduction in circulating estrogens may be a causative factor. Identification of an influence of menopausal status on bariatric surgery outcome might help inform patients' choice of bariatric-surgery type. It would also be clinically useful given the high degree of variation in bariatric-surgery outcome, which is currently not well understood. For example, in Sjostrom's [19] summary of the Swedish obesity study, postoperative weight loss at 10 y post-surgery ranged from –61 kg (i.e., 61 kg weight *gain*) to 106 kg weight loss.

Future work should address several weaknesses of our study. Most importantly, because we used a surrogate measure of menopausal status, it is necessary to establish that the effects we observed were in fact due to menopausal status rather than age *per se*. However, if age were to have an independent affect on bariatric surgery outcome, its influence would appear to be limited to women > 45 y of age; we failed to detect any difference in analyses of 20-25 vs. 30-35 y old women, 30-35 vs. 40-45 y old

women, and 20-25 vs. 40-45 y old women, all of which had adequate (> 0.8) statistical power. Future studies should also determine whether menopausal status affects gastric banding more than RYGB, as out data suggest. Because these two procedures differ in efficacy for weight loss [20-23], it may be that the effect of menopause is related to degree of weight loss rather than surgery type. It will also be important to determine whether menopausal status truly interacts with bariatric surgery to affect weight loss or metabolic health or whether the two effects simply add. Our data suggest that there may be a true interaction because the proposed effect of menopause on body weight appears rather small, suggesting that the gain in adipose tissue may be more or less balanced by a loss in lean body mass [7-10]. Finally, it will be important to consider a number of important variables that we were not able to include, such as insulin resistance, metabolic syndrome, and differences in psychiatric co-morbidities [24-28].

It should be noted that the potential measurement error introduced by the stratification of women by menopausal age rather than documented onset of menopause would serve to *reduce* the apparent effect of menopausal status on bariatric-surgery outcome. First, because about 5% of American women enter natural menopause before 45 y of age and 5% enter menopause after 55 y of age [29, 30], we may have misclassified the menopausal status of up to 10% of our sample. Second, a substantial percentage of women, about 10% of women < 45 y of age in one recent study [29], undergo surgical menopause; such patients would also have been misclassified. Third, because estrogens appear to mediate the effects of reproductive axis function on weight regulation, women who elected to receive postmenopausal hormone replacement therapy (HRT) should not have been considered together with

women who did not elect HRT. Thus, if there is an effect of menopausal status on bariatric surgery outcome, it is likely larger than that suggested in this study.

Interestingly, the effects that we detected increased in magnitude during the second year post-surgery. The range of reported postoperative weight change from surgery to 12 mo post-surgery is usually relatively small, as the vast majority of patients lose significant weight in a relatively linear fashion during the first year [19]. In contrast, large individual differences in weight loss emerge during the second year postoperatively. Thus, identifying factors that influence surgery outcome in this and later periods is especially important.

Much of the beneficial effect of bariatric surgery on appetite, weight loss and metabolic health is thought to be due to changes in the secretion of gut hormones, including ghrelin, cholecystokinin (CCK) and glucagon-like peptide-1 (GLP-1) [31-38]. Because estrogens powerfully regulate the potency of these hormones to control eating in rats [12, 39-41], these hormones are also likely causes for any influence of menopause on bariatric-surgery outcome suggested by our data. RYBG limits the exposure of gastric endocrine cells to ingesta, which should reduce preprandial ghrelin secretion, and bypasses the proximal duodenum, which should increase postprandial secretion of GLP-1, which is expressed more densely in distally located enterorendocrine cells. The mechanism through which gastric banding affects satiation is less clear but, as it does not seem not to depend on restriction alone, may also involve prandial gut hormone secretion [42].

In conclusion, we report the first evidence suggesting that menopausal status may affect bariatric-surgery outcome in women. Further study of the influences of

reproductive physiology on the weight-loss and metabolic-health outcomes of RYGB, gastric banding and other bariatric surgery procedures is warranted.

Disclosure The authors declare no conflict of interest.

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Figure 1. Percent excess body weight loss (%EBWL) 12 and 24 mo after gastric banding or Roux-en-Y gastric-bypass surgery, controlling for Pre-op %EBW in premenopausal-aged women and postmenopausal-aged women. By 24 mo after gastric banding, premenopausal-age women (n= 271) lost about 10% more weight than postmenopausal-age women (n = 54); there was no significant difference in premenopausal-age (n = 928) and postmenopausal-age (n = 103) women after RYGB.

* $p < 0.01$